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Factors Associated with Non-Response to Cardiac Resynchronization Therapy: Insights from a Real-World, Single-Center Study

Facteurs associés à la non-réponse à la thérapie de resynchronisation cardiaque : Aperçu d'une étude monocentrique en situation réelle

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Résumé

Contexte & objectifs. La thérapie de resynchronisation cardiaque (TRC) est proposée aux patients avec insuffisance cardiaque avec dysfonction ventriculaire gauche sévère symptômatique avec QRS large. Malgré ses avantages avérés, un pourcentage significatif de patients ne répond pas positivement à la TRC sur la base des critères évalués. L'objectif de la présente étude était de déterminer la fréquence de la non-réponse à la TRC et d'identifier les facteurs associés chez les patients souffrant d'insuffisance cardiaque et ayant bénéficié d'une implantation de TRC. *Méthodes.* Une étude de cohorte historique a été menée sur les patients atteints d'insuffisance cardiaque ayant reçu une TRC au Centre Hospitalier de Saint-Quentin (CHSQ) du 1er janvier 2020 au 30 septembre 2022. Les paramètres d'intérêt englobaient les données démographiques, cliniques, biologiques, électrocardiographiques, échocardiographiques et d'imagerie par résonance magnétique, des marqueurs biologiques et des résultats de suivi. La non-réponse à la CRT a été définie comme l'absence d'amélioration de la fraction d'éjection du ventricule gauche (FEVG) de plus de 10 % six mois après la CRT. La régression logistique multivariée a été utilisée pour rechercher les facteurs associés à la non-réponse à la TRC. *Résultats.* Sur 82 patients, 29 (35,4 %) ont été classés comme non-répondeurs. La FEVG moyenne est passée de 27,5 % à 40 % après la CRT. Les facteurs associés à la non-réponse comprenaient : la fibrose IRM (aOR=3.99 ; p=0.007), le sexe masculin (aOR=3.04 ; p=0.006), une dose initiale faible et moyenne de Sacubitril-valsartan respectivement

Summary

Context and objective. Cardiac resynchronization therapy (CRT) is applied to symptomatic treated patients with HFrEF and wide QRS. Despite its established benefits, a significant percentage of patients don't respond positively to CRT based on the assessed criteria. The aim of this study was to determine the frequency of CRT non-response and identify its associated factors among heart failure patients who underwent CRT implantation.

*Methods***.** A historical cohort study was conducted on heart failure patients who received CRT at the Saint-Quentin Hospital Center (CHSQ) from January 1, 2020, to September 30, 2022. The data collected included demographics, clinical characteristics, electrocardiographic, echocardiographic, and magnetic resonance imaging measurements, biological markers, and follow-up results. Non-response to CRT was defined as the failure to improve left ventricular ejection fraction (LVEF) by more than 10% six months after CRT. We used multivariate logistic regression analysis to identify variables independently associated with non-response to CRT.

*Results***.** Out of 82 patients, 29 (35.4%) were categorized as non-responders. Mean LVEF increased from 27.5% to 40% after CRT. Factors associated with non-response encompassed: MRI fibrosis **(**aOR=3.99; p=0.007), male sex (aOR=3.04; p=0.006), low and medium starting dose of Sacubitril-valsartan respectively (aOR=3.02; p=0.013; aOR=2.03; p=0.032) and history of ischemic cardiac

(aOR=3.02 ; p=0.013 ; aOR=2.03 ; p=0.032) et antécédents de cardiopathie ischémique (aOR=2.4 ; p=0.037). *Conclusion*. La non-réponse à la TRC est très fréquente et est attribuée aux antécédents spécifiques du patient, aux conditions cliniques, comportementales et physiopathologiques sous-jacentes. D'où l'importance d'améliorer la sélection des patients et de mettre en œuvre des stratégies de traitement personnalisées.
Mots-clés : Thérapie de resynchronisation cardiaque, insuffisance cardiaque, non-réponse, prédicteurs, échocardiographie, biomarqueurs.

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heart disease (aOR=2.4; p=0.037).

Conclusion. The non-response to CRT is common and is attributed to the patient's specific history, clinical, behavioral and underlying pathophysiological conditions. These findings underscore the importance of improving patient selection and implementing personalized treatment strategies. Future studies should focus on improving patient selection criteria, optimizing CRT techniques, exploring new biomarkers, assessing long-term outcomes and exploring innovative therapies.

Keywords: Cardiac resynchronization therapy, heart failure, non-response, predictors, echocardiography, biomarkers

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Introduction

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide, placing a significant burden on healthcare systems (1). Therapeutically, in addition to optimal medical treatment of HF (OMT), the European Society of Cardiology (ESC) guidelines recommend the implantation of CRT in patients with heart failure with interventricular desynchrony as branch block with wide QRS, who maintain LVEF ≤ 35 % and remain symptomatic despite a well-conducted OMT over 3 months (2).

CRT consists of the implantation of a biventricular pacemaker with or without a defibrillator option to resolve bundle branch block asynchrony to improve LVEF and improve quality of life of patients with HF. When the CRT device is a pacemaker comprising 2 biventricular pacing leads with or without an atrial lead, it is called a CRT-P; when the CRT device is a defibrillator the device is called a CRT-D. It is now the cornerstone of treatment of heart failure in patients with heart failure whose LVEF has been reduced and not improved by OMT (2). The majority of patients with HF have HFrEF, with many of them also experiencing intraventricular conduction disorders that can lead to interventricular asynchrony. In recent years, cardiac resynchronization therapy (CRT) has emerged as a crucial intervention for patients with HFrEF and bundle branch block (BBB) in addition to optimal medical therapy (OMT), addressing ventricular desynchrony (2-3). The COMPANION study, which compared OMT alone to OMT + CRT-P/D, showed that using CRT with or without a defibrillator in patients with advanced heart failure significantly reduced the rate of hospitalization for all causes. Since then, several other studies have confirmed the benefits of this treatment in improving clinical symptoms related to heart failure and reducing all-cause mortality (4-5). Despite the advancements and proven benefits of CRT, a notable subset of patients does not respond to this therapeutic approach, leading to suboptimal outcomes and ongoing symptoms (2, 6). The prevalence of non-response to CRT varies across different patient populations and clinical settings, typically ranging between 25% and 40% (3). This variability is influenced by a range of factors, including clinical characteristics, device settings, and underlying pathophysiological conditions (6). Numerous attempts have been made to identify reliable clinical and paraclinical markers that can

predict the response to CRT (7-9), with ongoing studies in progress. While these studies have identified several factors associated with successful resynchronization, a definitive predictor of CRT response remains elusive.
Understanding the determinants of non-response is crucial for optimizing patient selection, improving therapeutic strategies, and enhancing overall treatment outcomes (6, 10).
The Saint Quentin Hospital Center (SQHC), a prominent cardiac care facility, has been actively involved in the implantation and management of CRT devices. Furthermore, it functions as a benchmark institution for many hospitals in the Aisne region and portion of the Somme region. Providing services to a population of around 400,000 residents. Nevertheless, there is a scarcity of thorough data regarding the prevalence and determinants of non-response within this particular group. In order to fill this void, we carried out an historical cohort study with the objective of assessing the prevalence of non-response to CRT in heart failure patients implanted with CRT devices at the SQHC. Moreover, this study aims to investigate potential determinants associated with non-response to CRT, offering precious insights that could influence clinical practice and guide future research.

Methods

Study Design and Patients

Between January 1, 2020, and September 30, 2022, a comprehensive documentary study was undertaken on heart failure patients who had symptomatic chronic systolic heart failure (NYHA II–IV), decreased left ventricular ejection fraction (EF $\leq$ 35%), and a prolonged QRS (QRS $\geq$ 130 ms), and were undergoing CRT at the cardiology department of (CHSQ). The selection of CHSQ was based on its extensive cardiology services and its key position as a primary institution in the Aisne region, catering to almost 400,000 residents.

Implantation procedure and follow up

The implantations of devices were carried out by rhythmologists in accordance with the guidelines, using a transvenous approach (3). The right ventricular lead was attached either to the interventricular septum or to the right ventricular apex. The left probe was inserted into a lateral vein of the coronary sinus during a fluoroscopy-guided procedure. Once the probes were correctly placed, electrical parameters, including stimulation, detection, and impedance values, were recorded.
The objective pursued after resynchronization is to obtain on the ECG a refinement of the QRS and a change in the LV stimulation axis characterized by the appearance of a primodepolarization in D1-aVL and the appearance of a right block appearance.
Six months after his discharge from the hospital, the patient had an appointment for a follow-up consultation during which the following were taken: clinical parameters (weight, height), paraclinical parameters: ECG, Biology, parameters related to the functioning of the prosthesis (% of biventricular resynchronization) as well as data on the self-assessment of the patient's perception after CRT implantation.

Inclusion and Exclusion Criteria

Participant Selection

We conducted an analysis of the medical records of patients who had CRT-P/D at CHSQ for HFrEF with wide QRS and BBB appearance.
Patients who were admitted to the cardiology department of CHSQ during the study period for HFrEF care, received CRT, and had both baseline data and data from a 6-month follow-up were considered eligible for inclusion in this study.
Patients admitted for conditions other than heart failure, patients with heart failure with preserved EF, patients ineligible for CRT, patients who declined CRT, and patients in whom there was difficulty with the implantation of one of the two ventricular probes were excluded from the study.

Sample Size

We conducted a thorough sampling of patients who received CRT during the study period and met the inclusion criteria.

Technical Sampling

We first compiled a list of patients admitted for heart failure management. We then reviewed individual patient records to identify those who had received CRT. This subset of patients constituted our study population.

Independent Variables

The independent variables included socio-demographic information (sex, age, retirement status), clinical variables (family and personal history, anthropometric and clinical parameters such as weight, height, BMI, systolic blood pressure [SBP], diastolic blood pressure [DBP]), ECG parameters (rhythm, QRS duration, QRS morphology), echocardiographic Parameters

(LVEF and left ventricular [LV] diameter at baseline and at 6 months post-implantation), Cardiac Magnetic Resonance Imaging (MRI) (presence of myocardial fibrosis), CRT implantation parameters (site and position of probes), biological parameters (hemoglobin, NT-proBNP, creatinine, and estimated glomerular filtration rate [eGFR] at baseline and 6 months post-implantation), and functional assessment (quality of life and CRT tolerance at the 6-month follow-up).

Dependent Variables

The primary dependent variable was the response to CRT.

Research Methods

The data were gathered from the medical records of patients, encompassing clinical data extracted from patient charts, ultrasound data acquired from echocardiography reports prior to and 6 months following CRT implantation, electrocardiographic data obtained from digitized ECGs, and biological data included from laboratory results.

A consistent data collecting sheet was employed to record all relevant information. Data regarding quality of life were collected from consultation notes during the 6-month follow-up.

Operational Definitions

Responders and non-responders:

- The echocardiographic response was defined as an increase in LVEF beyond 10%, 6 months after CRT implantation.
- Echocardiographic non-response was defined as no increase in LVEF or an increase in LVEF less than 10%, 6 months after CRT implantation.

Statistical Analysis

Data were entered using Epidata version 3.1 and subsequently exported to SPSS version 25 for analytical procedures. Categorical variables are displayed as frequencies and percentages, while quantitative variables are summarized using measures of central tendency and variability. For variables that follow a normal distribution, the mean and standard deviation are reported; for those that do not follow a normal distribution, the median and interquartile range are provided. Multivariable logistic regression models were employed to explore the associations between baseline biology, lifestyle, clinical characteristics, ECG findings, echocardiography results, MRI data, and sociodemographic factors related to non-response. All variables demonstrating significance in the bivariate analysis were included in the final model. The optimal model was identified through the non-significant Hosmer-Lemeshow test. The variance inflation factor (VIF) was utilized to assess multicollinearity, with a threshold of greater than 5 indicating the presence of multicollinearity. Odds ratios (OR) along with their corresponding 95% confidence intervals were calculated to evaluate the strength of the associations. A p-value of less than 0.05 was established as the criterion for statistical significance in each analysis.

Ethics Approval and Consent to Participate

The data were collected anonymously and confidentially with respect to the privacy and personality of the patients. Confidentiality and ethics have been respected in accordance with the Helsinki Protocol. We ensured that the three fundamental principles of ethics were respected during the study: respect for the person, charity, and justice. This work had received approval from SQHC's Head of Cardiology Department prior to its initiation.

Results

General characteristics of the study population

The research sample consisted of 82 patients, with an average age of 71 ± 9 years. Among them, 50 (61.0%) were male and 32 (39.0%) were female, resulting in a sex ratio of 1.9 (in favor of males).

Frequency of Resynchronization Therapy Failure

Overall, among all patients who underwent CRT at SQHC during the study period, 29 (35.4%) were non-responders.

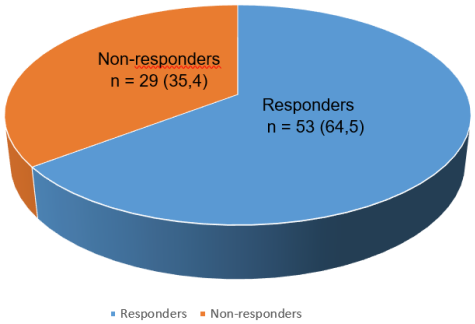

Figure 1. Patient outcome after CRT

General characteristics of participants overall and by response to CRT

Table 1 shows that dyslipidemia was the predominant cardiovascular risk factor among the patients examined, affecting 59 (72.0 %)

individuals. Hypertension was observed in 38 (46.9 %) patients, while diabetes mellitus was found in 29 (35.4 %) patients. The proportions of all evaluated cardiovascular risk factors were statistically comparable between responders and non-responders, with the exception of chronic renal disease, which was statistically more prevalent in non-responders than in responders.

The table reveals that the patients studied had a history primarily consisting of ischemic heart disease, dilated cardiomyopathy and atrial fibrillation, present in 48 (58.5%), 38 (48.3%) and 30 (36.6%) patients respectively. Ischemic heart disease was significantly less common in non-responders compared to responders. However, all other medical histories were found at statistically similar frequencies in both responders and non-responders.

Table 1 also shows that the duration of heart failure was less than 6 months for 29 (35.4%) patients, 6 to 12 months for 22 (26.8%) patients, 1 to 5 years for 19 (23.2%) patients, 5 to 10 years for 11 (13.4%) patients, and more than 10 years for 1 (1.2%) patient alone. There was no difference in the age of heart failure between non-responders and responders.

Table 1. General characteristics of participants overall and by response to CRT

	Overall n=82 (%)	**Non-responders n=29 (%)**	**Responders n=53 (%)**	**p**
Sex				
Male	50 (61)	22 (26,8)	28 (34,1)	0,034
Female	32 (39,0)	7 (8,5)	25 (30,5)	
Age (Mean ± SD) years	71,9 ± 8,8	73,0 ± 8,6	71,2 ± 8,9	0,316
< 65	21 (25,6)	6 (7,3)	15 (18,3)	
≥ 65	61 (74,4)	23 (28,0)	38 (46,3)	
Cardiovascular risk factors				
Diabetes	29 (35,4)	12 (14,6)	17 (20,7)	0,273
Chronic kidney disease	23 (28,0)	12 (14,6)	11 (13,4)	0,043
Obesity	25 (30,5)	9 (11,0)	16 (19,5)	0,564
Hypertension	38 (46,9)	13 (16,0)	25 (30,9)	0,481
Dyslipidemia	59 (72,0)	21 (25,6)	38 (46,3)	0,579
Cigarrette smoking	25 (30,5)	9 (11,0)	16 (19,5)	0,732
Excess alcohol intake	25 (30,5)	10 (12,2)	18,3 (53)	0,368
Medical history				
Atrial fibrillation	30 (36,6)	12 (14,6)	18 (22,0)	0,333
Cancer	7 (8,5)	1 (1,2)	6 (7,3)	0,216
Ischemic heart disease	48 (58,5)	21 (25,6)	27 (32,9)	0,048
Myocardial fibrosis (n=37)	12 (31,9)	6 (15,8)	6 (15,8)	<0,001
Chronic respiratory disease	21 (25,6)	10 (12,2)	11 (13,4)	0,137
Chronic kidney disease under Dialysis	7 (8,5)	3 (3,7)	4 (4,9)	0,478
Sleep apnea syndrome	24 (29,3)	7 (8,5)	17 (20,7)	0,311
Age of heart failure				0,485
< 6 months	29 (35,4)	11 (13,4)	18 (22,0)	
6-12 months	22 (26,8)	5 (6,1)	17 (20,7)	
1-5 years	19 (23,2)	8 (9,8)	11 (13,4)	
5-10 years	11 (13,4)	6 (7,3)	6 (7,3)	
>10 years	1 (1,2)	0 (0,0)	1 (1,2)	
therapeutic on the starting prescription				
Entresto (Sacubitril-valsartan)	56(68.3)	35(66.0)	21(72.4)	0.368
Entresto Dose				0.015

Low dose	6(10.7)	1(2.9)	5(23.8)	
Mean dose	34(60.7)	21(60.0)	13(61.9)	
Maximum dose	16(28.6)	13(37.1)	3(14.3)	
BB	81(98.8)	52(98.1)	29(100.0)	0.646
iSGLT2	76(92.7)	48(90.6)	28(96.6)	0.303
MRA	58(70.7)	37(69.8)	21(72.4)	0.507
ACEI/ARB	25(30.5)	18(34.0)	7(24.1)	0.253
Diuretic	56(68.3)	37(69.8))	19(65.5)	0.436
Physical examination	80,4 ± 18,9	81,7 ± 22,12	79,8 ± 17,16	0,662
Weight in Kg (X±DS)	167,5 ± 8	171,4 ± 8,4	161,4 ± 8,7	0,415
Hight in Cm (X±DS)	28,6 ± 5,7	28,8 ± 7,26	28,5 ± 4,8	0,836
BMI in Kg/m^2 (X±DS)	28,6 ± 5,7	28,8 ± 7,26	28,5 ± 4,8	0,836
SBP prior CRT in mmHg (X±DS)	130,3 ± 25,6	132 ± 24,61	129,4 ± 23,2	0,007
DBP prior CRT en mmHg (X±DS)	77,3 ± 12,9	79,9 ± 13,4	75,9 ± 12,52	0,072
SBP after CRT in mmHg (X±DS)	129,5 ± 16,9	124,7 ± 13	127,4 ± 18,7	0,234
DBP after CRT in mmHg (X±DS)	75,9 ± 11,1	76,4 ± 10,2	75,8 ± 11,6	0,054
Duration of hospitalization in day (X±DS)	3,4 ± 0,77	3,4 ± 0,82	3,53 ± 0,74	0,123

Kg: Kilogram; kg/ m^2: kilogram per square meter; SBP: systolic blood pressure; DBP: diastolic blood pressure; (X±SD): typical mean ± deviation; Cm: centimeter, CRT: cardiac resynchronization therapy, BMI: body mass index; NR: Not specified.

We also observed in the same table that before CRT, non-responders had a statistically higher systolic blood pressure compared to responders. However, the systolic blood pressure after CRT was statistically comparable between responders and non-responders. Additionally, all other physical examination parameters were similar before and after resynchronization for both groups. At baseline, the majority of patients had all 4 classes of medicinal products recommended for the treatment of chronic HF (beta-blockers, ARB2/ACE-inhibitors/Entresto, ISGLT2, MRA). MRI fibrosis was found in 32% of the population having undergone cardiac MRI and was statistically comparable in the 2 populations. The most commonly prescribed treatment group was BB on almost all prescriptions 81 (98.8), followed by ISGT2 76 (92.7 %), MRA 58 (70.7%), and Entresto 56 (68.3 %). Only 30% of patients had a loop diuretic in their treatment. Comparing the prescription therapy at baseline and response to CRT, the 4-heart failure therapeutic classes were statistically comparable in the 2 groups; however, non-responders had significantly lower doses of Entresto on their prescription at entry (p=0,015).

Evolution of the studied paraclinical parameters according to the response to the CRT

The table 2 below compares the different variables at intake and at 6 months after cardiac resynchronization according to CRT response. The results show that: the mean LVEF increased after resynchronization in the 2 populations. LVDD was significantly decreased after resynchronization, with a more pronounced decrease in responders. The decrease in natriuretic peptides was observed in the 2 populations, but significantly more marked in the responders. After resynchronization, there was a slight decrease in GFR, which was statistically more pronounced in responders (p=0.046); the change in LV stimulation axis characterized by primo-negativity to D1-aVL associated with right block appearance was statistically more pronounced in responders compared to non-responders (p=0.012).

Table 2. Population distribution by CRT response and echocardiographic, ECG and laboratory data

Variable	Before CRT			After CRT		
	Answer (n=53)	Non-response (n=29)	P	Answer (n=53)	Non-response (n=29)	p
QRS Duration (ms)	172.7±12.9	169.6±13.8	0.193	150.0±12.0	152.9±13.4	0.462
<150	3(5.7)	4(13.8)		28(52.8)	13(44.8)	
150-170	16(30.2)	12(41.4)		23(43.4)	13(44.8)	
>170	34(64.2)	13(44.8)		2(3.8)	3(10.3)	
LVEF (%)	25.2±5.9	28.9±6.4	**0.047**	42.3±6.9	36.6±6.5	**0.001**
≤15	4(7.5)	2(6.9)		-	-	
16-30	43(81.1)	17(58.6)		4(7.5)	7(24.1)	
31-40	6(11.3)	10(34.5)		20(37.0)	15(53.6)	
41-50				25(46.3)	6(21.4)	
>50				5(9.3)	0(0.0)	
DTDVG (mm)	65.8±5.2	66.7±4.7	0.793	60.1±4.3	62.0±5.2	**0.042**
<65	20(37.7)	9(31.0)		47(88.7)	20(69.0)	
65-75	30(56.6)	19(65.5)		6(11.3)	8(27.6)	
>75	3(5.7)	1(3,4)		0(0.0)	1(3,4)	
NT-ProBNP (pg/ml)	1742.0(1437.0-1843.0)	1591.0(1190.2-1869.9)	0.896	254.0(182.5-327.0)	540.0(290.0-835.0)	**0.020**
<600	1(1.9)	1(3,4)		39(73.6)	15(51.7)	
600-1000	9(17.0)	7(24.1)		13(24.5)	9(31.0)	
1001-00	29(54.7)	14(48.3)		1(1.9)	5(17.2)	
>2000	14(26.4)	7(24.1)		0(0.0)	0(0.0)	
eGFR (ml/min/1.73 m^2)	52.2(43.1-62.0)	49.2(46.3-58.3)	0.562	48.5(44.5-58.0)	43.7(40.1-47.7)	**0.046**
≥60	22(41.5)	9(31.0)		17(32.1)	4(13.8)	
59-30	25(47.2)	15(51.7)		33(62.3)	19(65.5)	
<30	6(11.3)	5(17.2)		3(5.7)	6(20.7)	
Hb (g/dl)	13.1±1.7	12.7±2.4	0.431	13.5±4.2	12.5±1.7	0.253
Rhythm			0.934			0.167
Sinusal	37(69.8)	21(72.4)		48(90.6)	14(48.3)	
FA	11(20.8)	5(17.2)		7(13.2)	13(44.8)	
Electro-driven	5 (9.4)	3(10.3)		49(92.5)	29(100.0)	

Spontaneous		4(7.5)	0	
QRS refinement		27.0 (21.5-29.0)	21.0(12.0-23.0)	0.291
<0ms		3 (5.7)	6 (20.6)	
0-20ms		15 (28.3)	7 (24.1)	
21-40ms		28 (52.8)	14 (48.3)	
>40ms		7 (13.2)	2 (6.9)	
D1, aVL, and BBD first-line negation				**0.012**
No		16 (30.2)	17 (58.6)	
Yes		37 (69.8)	12 (41.4)	
% of QRS refinement after CRT: Median (EIQ)		15 (9-20)	12 (5-16)	**0.036**
<15		29 (54.7)	22 (75.9)	
15-30		20 (37.7)	7 (24.1)	
30-50		2 (3.8)	0	
>50		2 (3.8)	0	

LVEF: left ventricular ejection fraction, LVEDD: left ventricle and diastolic diameter, eGFR: glomerular filtration rate, Hb: hemoglobin, RBB: Right bundle branch bloc.

Implantation data for participants overall and based on CRT response

As depicted in table 3, a significantly higher number of responders were found to have a resynchronization percentage of 90% or higher compared to non-responders. The position of the right ventricular (RV) probe was predominantly septal rather than apical in the entire population studied. Non-responders had the RV probe in the apical position more often than responders, while responders had it in the septal position more frequently than non-responders. No differences between non-responders and responders were noted regarding other site settings.

Table 3. Implantation data for participants overall and based on CRT response

	Overall n=82 (%)	**Non-responders n=29 (%)**	**Responders n=53 (%)**	**P**
Resynchronization percentage (X ± DS)	78,8 ± 9,7	74,9 ± 8,05	81,03 ± 9,9	0,01
<80	42 (51,2)	19 (65,5)	23 (43,4)	
80-89	25 (30,5)	9 (31,2)	16 (30,2)	
≥90	15 (18,3)	1 (3,4)	14 (26,4)	
Approach way				0,368
Céphalic and SC	57 (69,5)	19 (23,2)	38 (46,3)	
SC alone	25 (30,5)	10 (12,2)	15 (18,3)	
Position of RV pacing lead				0,008
Septale	55 (67,1)	14 (17,1)	41 (50,0)	
Apicale	27 (32,9)	15 (18,3)	12 (14,6)	
Position of LV pacing lead				0,354
V. latérale	81 (98,8)	28 (34,1)	53 (64,6)	
V. antérieur	1 (1,2)	1 (1,2)	0	
Number of probes				0,397
AVV	73 (89,0)	25 (30,5)	48 (58,5)	
2VV	9 (11,0)	4 (4,9)	5 (6,1)	

SC: coronary sinus; RV: right ventricle; LV: left ventricle; (X±SD): typical mean ± deviation; AVV: two ventricular leads (left and right) and one right atrial lead; 2 VV: two ventricular leads.

Factors associated with non-response to CRT

As shown in Table 4, after adjustment in the multivariate analysis, it was found that the risk of non-response to resynchronization was doubled in men, patients with a history of atrial fibrillation, and those with myocardial fibrosis on MRI. The risk was quadrupled in smoking patients.

Table 4. Factors associated with non-response to CRT

Variable	**Bivariate analysis**		**Multivariate analysis**	
	P	OR (95% CI)	P	aOR (95% CI)
Sex				
Female		1		1
Male	**0.015**	2.81(1.03-4.68)	**0.006**	3.04 (2.85-6.17)
CKD				
No		1		1
Yes	**0.005**	2.70 (1.99-3.28)	0.538	1.74 (0.30-3.14)
Dose of Sacubitril-valsartan				
Maximum		1		1
Average	**0.018**	2.68 (1.64-4.25)	**0.039**	2.03 (1.16-3.71)
Weak	**0.015**	3.67 (2.80-6.57)	**0.013**	3.02 (2.52-5.41)
Statin				
No		1		1
Yes	**0.041**	2.34 (1.88-4.22)	0.372	2.10 (0.41-4.87)

Ischaemic heart disease				
No		1		1
Yes	**0.026**	2.53 (1.95-4.71)	**0.037**	2.40 (1.36-3.11)
MRI fibrosis				
No		1		1
Yes	**0.002**	3.40 (1.89-7.46)	**0.007**	3.99 (2.67-5.04)

CKD : Chronic kidney desease

Discussion

We performed a retrospective analysis involving 82 patients, aged 71 ± 9 years, composed of 61% men and 39% women. The objective of our study was to assess the frequency and identify factors associated with non-response to CRT in heart failure patients implanted at the SQHC We found a significant rate of non-response to CRT, with specific clinical, behavioral and underlying pathophysiological conditions influencing CRT response.

Cardiac resynchronization therapy (CRT) represents a cornerstone in the management of heart failure (HF) patients with left ventricular desynchrony (2-3). Despite its broad application and proven cost-effective (11-12) morbidity and mortality benefits (13-14), a considerable fraction of patients fail to respond to CRT (2, 6). Our study provides valuable insights into the prevalence of CRT non-response and identifies determinants that may influence the efficacy of this treatment.

Prevalence and Patient Characteristics

The CRT non-response rate of 35.4% found in our study is consistent with previous research (6, 15-17) that indicates around 30% and 37% of CRT recipients are non-responders. This finding highlights the ongoing challenge in identifying patients who will not benefit from this therapy.

This result is lower than that found by Martina N *et al.* (16), who reported a non-response rate of around 40%. This difference is mainly explained by the different definitions of non-response used in the studies mentioned above. However, it highlights the fact that, despite differences in the definition of non-response to CRT, the proportion of individuals showing no response to CRT varies among different studies, usually ranging between 25% and 40% (3, 15-16).

The literature portrays a notable disparity in the rate of non-response to CRT. The variability seen may be attributed to the significant heterogeneity in the definitions utilized to characterize CRT, together with the wide range of clinical, anatomical, and electrophysiological characteristics of the individuals included in the research (6). It is worth noting that there is a lack of consensus on the precise definition of a CRT responder or non-responder, resulting in a criticism of the concept itself (18). The determination of non-response is sometimes established using arbitrary remodeling thresholds, such as a decrease in left ventricular end-systolic volume exceeding 10% to 15% from initial measurement, or increased LVEF or end-diastolic diameter. It is important to note that these limitations may not necessarily indicate a lack of improvement in challenging clinical outcomes (18). Furthermore, there is also no agreement on the appropriate timing for assessing the response to CRT (19-20).

Echocardiographic characteristics appear to be the most effective in clearly identifying the response to CRT. Rickard *et al*. showed that the survival benefit following CRT is highly associated with the degree of improvement in ventricular function as assessed by echocardiography (21). Non-response in our study was defined as the lack of a rise in the LVEF beyond 10 percent the during 6-month follow-up period. The demographic composition of our study population, characterized by an average age of 71 years and a predominance of males, aligns with the typical heart failure population (1, 22). Although non-responders had a higher incidence of chronic renal disease, there were no notable disparities between responders and non-responders in terms of other cardiovascular risk factors, including dyslipidemia, hypertension, and diabetes mellitus. These results emphasize that although some risk factors may be more common among those who do not respond, they are not solely predictive of CRT response.

Clinical and Electrocardiographic Parameters

We found that non-responders had a higher systolic blood pressure before CRT, but the post-CRT systolic blood pressure was comparable in both groups. Thus, it appears that baseline blood pressure may not be a dependable indicator of the

effectiveness of CRT. However, its influence on the CRT response should be explored more.

The primary goal of CRT implantation is to achieve resynchronization. The presence of a change in the stimulation axis and the improvement of the QRS are indicators of successful resynchronization on the EKG. Therefore, the absence of these features may suggest a lack of resynchronization in certain cases. The present study found that non-responders exhibited a reduced frequency of initial negation in the D1 and aVL leads, as well as right bundle branch block aspect (RBBBA) after CRT, compared to responders. However, our investigation did not find any ECG measures that might independently predict non-response to CRT. These findings support the existing understanding that although specific ECG markers can offer information about the effectiveness of CRT, no individual EKG characteristic is reliable enough to predict treatment results alone (23). This highlights the intricate nature of CRT response, which is likely influenced by a variety of factors outside of basic EKG criteria. Further investigation of additional EKG characteristics would be advantageous in enhancing the prediction of both CRT response and non-response.

Echocardiographic, Biological, and Clinical Parameters

Significantly, although non-responders exhibited higher left ventricular ejection fraction (LVEF), higher creatinine levels, lower hemoglobin levels before CRT, and higher NT-proBNP levels in comparison to responders, the logistic regression analysis showed no association between these factors with non-response to resynchronization. This lack of a distinct association suggests that although differences exist in baseline and post-treatment biomarkers between responders and non-responders, these factors alone may not completely explain the variability in CRT outcomes. The results of our study are consistent with those reported in the literature. In instance, *Brenyo A. et al.* (24) conducted a study that assessed the role of BNP in CRT and found that most patients who had high BNP levels after resynchronization did not respond to this therapy. In a substudy of CARE-HF, Berger *et al.* (24) reached a similar finding about the predictive significance of BNP.

Clinical Self-Assessment and Device Parameters

One notable finding was that a smaller percentage of those who did not respond reported clinical improvement after CRT compared to those who indeed responded. This subjective evaluation supports the objective evidence, strengthening the idea that those who do not respond to CRT perceive less clinical utility. Although ultrasound findings indicate no response, a subset of individuals who did not respond report functional improvement. This finding emphasizes the placebo effect observed in patients who have undergone CRT, which explains the low occurrence of non-response when the evaluation of response is based on clinical factors, as emphasized by certain research studies (25). In terms of device implantation factors, the placement of the RV pacing lead appeared to impact CRT response. Non-responders had a greater frequency of placing the apical pacing lead. The absence of an independent association between pacing leads position and CRT non-response in this study may be attributed to the fact that, unlike conventional stimulation, the response of the CRT is not determined by the position of the right probe only. Instead, it is the combination of the RV and LV probes that is linked to the response (45).

Determinants of non-response

Several important factors associated with CRT non-response were identified in our study. The presence of myocardial fibrosis on MRI increased the risk of non-response by 4-fold; male gender increased the risk of non-response by 3-fold; low and medium dose of Entresto at initial treatment increased the risk of CRT non-response by 2-fold and 3-fold respectively; history of ischemic heart disease increased the risk of non-response by 2-fold.

Male sex is a factor associated with poor response to CRT in several studies. (31,37-40) Our study found that men tripled the risk of not responding. Our results are in line with those reported in the literature (29-31) Evidence shows that men are implanted more often with a CRT device than women, but that women generally achieve much better treatment outcomes after CRT than men (23,26,37) The reasons of the gender disparity in the actual CRT implantation rates are still uncertain. In the study by *Lilli et al.* (29) only 19.7% of the 334 patients who did not respond to CRT were female. In the same study, compared to men, women had a markedly higher

decrease in LVD and a lower frequency of non-response (23.9 vs 40.7%, P < 0.05).

Female gender was identified as an independent predictor of long-term survival after CRT (28). This disparity is thought to be attributed exclusively to the higher probability of nonischemic heart disease and left bundle branch block in women, which tends to predict the efficacy of CRT. In contrast, men are more prone to ischemic heart disease. However, while there is increasing evidence to suggest that the benefits of CRT may be more significant in women than in men, women are still less likely than men to benefit from CRT treatment.

Our study identified ischemic heart disease as a risk factor for non-response, in the sense that it increased the risk of non-response by 2-fold. Our observations are similar to those found by *Aysha Arshad et al*. (31) who in a study that assessed CRT response in both sexes found that patients with ischaemic heart disease appeared to derive less benefit from CRT compared to those without ischaemic heart disease. Our results are contrary to those reported by *Pezel et al.* (17) and *Juan C. Plata-Corona et al*. (39) who found that ischaemic heart disease was not a factor associated with non-response. the CRT results in patients with ischaemic heart disease appear to be contradictory, the explanation for this difference of opinion may be explained by the fact that ischaemic heart disease alone does not always explain the CRT results but that the location of the scar, its size and its relationship to the implanted stimulation electrodes may be the cause of this discordance (23).

The risk of non-response was three times higher in patients with myocardial fibrosis discovered on MRI. This is consistent with the results reported by *Massoulli et al.* (35), which indicate that a lower degree of cardiac fibrosis is associated with a favorable response after CRT implantation. Previous studies have shown that a higher percentage of fibrosis and a higher percentage of transmural extension of the myocardial scar, as assessed by MRI, are associated with a poor response to biventricular stimulation, regardless of the aetiology of heart failure (40-41) These studies highlight the importance of performing MRI or laboratory evaluation of cardiac fibrosis prior to CRT implantation, in addition to using traditionally well-established predictors. However, the use of MRI in everyday practice for any patient remains difficult, it is not very available, it is expensive and it requires specific clinical expertise. It is now known that myocardial scarring not only alters the reverse remodeling of the left ventricle, but is also a substrate for severe ventricular arrhythmias that can result in sudden death (41-42). However, this observation is contrary to that described by other authors who have found that myocardial fibrosis was not an element of poor response to CRT (17,25). This difference can be explained by the heterogeneity of the percentage of ventricular fibrosis and the heterogeneity of its distribution in the left ventricle; but also, by the definition of the non-response related to fibrosis on MRI. This emphasizes the fact that myocardial fibrosis alone cannot be a factor limiting the implantation of CRT. Therefore, there is a real need for studies in the future to establish strong criteria that can predict non-response to CRT using MRI criteria to optimize response to this therapy. Non maximal dose of Entresto in the initial regimen was associated with the risk of non-response to CRT. This association has not been found in the literature. However, it's may provide evidence that optimal treatment prior to CRT implantation increases the likelihood of responding to CRT; it should be noted that most studies that assessed response to CRT compare patients with CRT in combination with OMT and those on OMT alone (43-44). Optimal treatment is therefore an important prerequisite before the CRT is implanted.

Strengths and Limitations

This study should be interpreted within the context of its strengths and potential limitations.

Strengths of the study include: (1) Real-World Data from a Specific Institution, mimicking routine clinical practice and potentially bridging the gap between controlled clinical studies and everyday patient treatment (2). Comprehensive Dataset, with a wide range of clinical, electrocardiographic, MRI, echocardiographic, and biological characteristics, allowing for a multidimensional assessment of CRT response. This comprehensive approach contributes to capturing a holistic understanding of the factors driving CRT efficacy.

Limitations of the study include : Single-center study with limited sample size: carried out in a single clinical institution, so restricting the capacity to apply findings to other settings with different patient populations, clinical procedures, and device management ; the retrospective design

of the study relies on existing patient data, which may create bias and restrict the capacity to prove causality ; Selection bias: the particular patient features of the SQHC may not accurately reflect the broader heart failure population, thereby impacting the accuracy of results ; and Insufficient duration of follow-up: the study's relatively brief follow-up time does not evaluate the long-term results or durability of the beneficial effects of CRT.

Conclusion

The present study offers a thorough evaluation of CRT non-response and reveals several variables that may influence the outcome. The substantial non-response rate highlights the need of improving patient selection and customizing treatment regimens. The correlation between non-response and variables such as male sex, history of atrial fibrillation, myocardial fibrosis on MRI, and smoking suggests that a holistic strategy, taking into account both individual patient characteristics and procedural aspects, could enhance treatment outcomes for CRT. Future studies should focus on improving patient selection criteria, optimizing CRT techniques, exploring new biomarkers, assessing long-term outcomes and exploring innovative therapies.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

KMC wrote the first draft of the manuscript; AD revised manuscript and were one of implanters of rhythm prostheses; TBM and LLG prepared the database and carried out the statistical analyses; MM, OON, SMY, MRJ, MST, OOR, MMB, KMF, revised manuscript; LMB, MKJ and KPB were scientific coordinator of the work.

Ethics approval

All experiments were performed in accordance with relevant guideline and regulations of Declaration of Helsinki. Data was fully anonymized before being accessed and the source of data was made from patient records.

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